REMARKS

The fee for the three month extension of time and any fees that may be due in connection with the filing of this paper or during the entire pendency of this application, may be charged to Deposit Account No. 02-1818. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

An Information Disclosure Statement has been filed under separate cover on the same day herewith. A change of correspondence address was filed with the Information Disclosure Statement.

Claims 1-7, 9-28, 30-50, 53-67 and 79-91 are pending in this application. Claims 12-14, 19-27, 39-50, 56-67, 80, and 82-89, which withdrawn from consideration as non-elected, are retained as they are linked by pending claims. Upon allowance of any linking claims, the restriction requirement as to any linked claims will be withdrawn. Claims 1 and 28 are amended to delete the extraneous word "evolved" and other redundant or extraneous language and to render it clear that the methods involve separately expressing a plurality of proteins, each of which differs by one amino acid from the target protein. The claims do not read on mutating one amino acid in a protein and replacing it with a one amino acid. Claims 90 and 91, which find basis as alternative embodiments in claim 1, are added.

THE REJECTION OF CLAIMS 1-11, 15-18, 28-38, 51-55 AND 79-81 ARE REJECTED UNDER 35 U. S. C. 112, SECOND PARAGRAPH

Claims 1-11, 15-18, 28-38, 51-55 and 79-81 are rejected under 35 U. S. C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention for reasons enumerated and discussed below. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

Paragraph 2 of section 112 requires that the "specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Courts have recognized since the requirement that one's invention be distinctly claimed became part of the patent law in 1870, the primary purpose of the requirement is "to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights." General Electric Co. v. Wabash Appliance Corp., 304 U.S. 364, 369 (1938). See, e.g., McClain v. Ortmayer, 141 U.S. 419, 424 (1891) ("The object of the patent law in requiring the patentee

[to distinctly claim his invention] is not only to secure to him all to which he is entitled, but to apprise the public of what is still open to them."); Rengo Co. v. Molins Mach. Co., 657 F.2d 535, 551 (3d Cir.) ("Its purpose is to demarcate the boundaries of the purported invention, in order to provide notice to others of the limits beyond which experimentation and invention are undertaken at the risk of infringement.") (internal quotation omitted), cert. denied, 454 U.S. 1055 (1981); Hoganas AB v. Dresser Indus., 9 F.3d 948, 951, 28 USPQ2d 1936, 1939 (Fed. Cir. 1993) (function of claims is "putting competitors on notice of the scope of the claimed invention").

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite. Rosemount Inc. v. Beckman Intstruments, Inc., 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983).

The purpose of 35 U.S.C. §112, second paragraph, is to provide those who would endeavor, in future enterprise, to approach the area circumscribed by the claims of a patent, with adequate notice demanded by due process of law, so that they may readily and accurately determine the boundaries of protection involved, evaluate the possibility of infringement and dominance by determining the metes and bound of protection so one can evaluate the possibility of infringement with a reasonable degree of certainty. In re Hammack, 427 F.2d 1378, 166 USPQ 204 (CCPA 1970).

Furthermore, claims are not to be read in a vacuum, and the limitations therein are to be interpreted in light of the specification, giving them their broadest reasonable interpretation.

Antecedent basis

"Obviously, however, the failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. Ex parte Porter, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Inherent components of elements recited have antecedent basis in the recitation of the components themselves. For example, the limitation "the outer surface of said sphere" would not require an antecedent recitation that the sphere has an outer surface." M.P.E.P. § 2173.05(e). Relevant law avoids an absolute requirement for antecedent basis when the when the specific context is clear. Just as "the outer surface of

said sphere" is clear, the cytoplasm of the cell is clear. Applicants submit that the context of "the cytoplasm" in the phrase "the cytoplasm of the cells" is clear to one of skill in the art.

Analysis

a. Claim 1 is rejected as failing to provide proper antecedent basis for "the evolved predetermined property or activity" in line 4 because line 2 recites "predetermined property or activity" rendering the antecedent for "the evolved predetermined property or activity." Amendment of claim 1 to delete "evolved" in line 4 obviates this alleged ambiguity.

b. Claim 1, line 16 and claim 28, line 14, are alleged to be indefinite in the recitation of "a restricted subset" because it allegedly is unclear this restricted subset is the same restricted subset as that recited in line 15 of claim 1 and lines 12-13 of claim 28, or a different restricted subset. Applicant respectfully disagrees.

Each of claims 1 and 28 recite:

> . . . the replacement amino acids comprise all of the 19 remaining non-native amino acids or a restricted subset of amino acids up to all 19 remaining amino acid; and
>
> a restricted subset is a group of selected amino acids selected to have a predetermined effect on protein activity . . .

In this wherein clause, these claims recite what the replacement amino acids include. Among the choices is a restricted subset. The **next phrase** describes what is meant by a restricted subset in general. There is no need to reference any antecedent nor is there any reason to doubt that a the identical term used twice in a claim would have two different meanings. ". . .[T]he failure to provide explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite. Ex parte Porter, 25 USPQ2d 1144, 1145 (Bd. Pat. App. & Inter. 1992) ("controlled stream of fluid" provided reasonable antecedent basis for "the controlled fluid"). Furthermore, there is no reason in the specification or the claims to ascribe two different meanings to the same term.

In this instance, it is clear that the wherein clause describes what a restricted subset encompasses.

THE REJECTION OF CLAIMS 28 AND 30-35 UNDER 35 U.S.C. §102(e)

Claims 28 and 30-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Winter (U.S. Patent No. 6,548,640) because claims 28 and 30-35 allegedly are drawn to a method for generating proteins with a desired property or activity produced by generating

mutants of a protein, and inserting into host cells nucleic acids which encode for the mutant proteins and:

> Winter studies altered antibodies that have a heavy or light chain variable domain in which the framework regions differ from the framework regions naturally associated with the complementarity determining regions of the variable domain and in which the framework regions are derived from the source of framework regions that differs from the framework regions naturally associated with the complementarity determining regions of the variable regions.

The Examiner continues and states that Table 3 in column 20 of Winter, antibodies are studied and "*altered to assess activity towards antigen*" and that the Winter discloses identifying residues in a target protein *in silico* that are associated with the property, and then replacing two of them with different amino acids. The Examiner states that Winter describes the use of an *in silico* generated representation of the loop of Phe27 to Tyr35 in the heavy chain variable domain of the human myeloma protein KOL, which is crystallographically solved and mutates Ser27 is selected to be mutated to Phe and Ser30 to Thr. The Examiner states that Winter then prepares nucleic acid molecules encoding variant proteins that differ by one replacement amino acid at one is-HIT locus from the target protein, separately expressing each variant. The second and third steps of the instantly rejected claims are described in Winter in column 19, line 62 to column 20, line 7, which states:

> In stage 1, the pSVgpt vectors HuVHCAMP-RaIgG2B, and also two mutants for reasons to be explained below, HuVHCAMP(Ser27 to Phe)-RaIgG2B, HuVHCAMP(Ser27 to Phe, Ser30 to Thr)-RaIgG2B) [sic] were introduced into the heavy chain loss variant of YTH34.5HL. In stage 2, the pSVgpt vectors RaVHCAMP-RalgG2B, RaCVHCAMP-HuIgG1, RaVHCAMP-HulgG2, RaVHCAMP-HuIgG3, RaVHCAMP-HulgG4 were transfected as described above. In stage 3, the pSV-gpt vector Hu(Ser27-Phe, Ser30-Thr)VHCAMP-HulgG1 was cotransfected with the pSV-neo vector HuVLCAMP-HuIgK into the rat myeloma cell line YO (Y B2/3.0 Ag 20).

The Examiner states that the encoded proteins are expressed; each vector encoding either the original or mutant protein. The amino acid serine is replaced with the amino acid phenylalanine, thus phenylalanine constitutes a "restricted subset" of amino acids used to replace the original amino acid in the unmodified protein. All of the single mutant proteins contain the same Ser27 to phenylalanine replacement. The Examiner continues and states that Table 3 of Winter in column 20 lists the results of screening the respective antibody proteins for antigen binding. Specifically, Table 3 illustrates the concentrations of antibody in μg/ml at 50% binding or lysis. In the original protein, concentration of 27.3 μg/ml is required for 50% binding while in the mutant proteins (Ser27 to Phe), 1.8 μg/ml is required for 50% binding. Consequently, the mutant LEAD protein has a much higher affinity for antigen as the original protein. Column 14, lines 52-59 and column 20, line 66 to column 22, line 12

indicate a predetermined change of binding to antigen upon mutating such residues in the "hypervariable region" including Ser27 and Ser30. Thus, the Examiner urges that Winter provides a method in which a property of a protein is evolved to a predetermined property, and premises the remainder of the rejection on the assertion that a restricted subset reads on a single amino acid change. This rejection respectfully is traversed.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). A reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

The Rejected Claims

Claim 28 recites:

> A high throughput method for generating proteins with a desired property or activity, comprising:
>
> (a) identifying residues in a target protein in silico that are associated with the property, and designating the loci of such residues is-HIT target loci;
>
> (b) preparing variant nucleic acid **molecules encoding variant proteins**, wherein:
>
> each variant nucleic acid encodes a candidate LEAD mutant protein that differs by one replacement amino acid at one is-HIT target locus from the target protein;
>
> the amino acid residues at each of the identified is-HIT target loci in the target protein is replaced with all of the non-native amino acids, or the amino acid residues at each of the identified is-HIT target loci in the target is replaced with a restricted subset of the remaining 19 non-native amino acids; and

a restricted subset is a group of selected amino acids selected to have a predetermined effect on protein activity;

(c) **separately** introducing the nucleic acid molecules encoding each candidate LEAD protein into hosts for expression thereof, and expressing the nucleic acid molecules encoding each variant protein to produce **sets of candidate LEAD proteins**, wherein:

each candidate LEAD protein in a set contains the same amino acid replacement;

each candidate LEAD protein contains a single amino acid replacement, and differs from the target protein by one amino acid replacement; and

each replacement is at the same locus; and

(d) **individually** screening each set of variant LEAD candidate proteins to identify any that have an activity or property that differs by a predetermined amount from the activity of the unmodified target protein, thereby identifying proteins that are LEADs.

Thus, in the instantly claimed methods residues for modification (is-Hit residue) in a protein is/are identified *in silico*, a plurality of variant polypeptides containing only a single amino acid change at an is-Hit locus are separately produced by introducing and expressing encoding nucleic acid molecules into cells to separately produce variant proteins, and each protein is separately screened to identify LEADs, which exhibit an activity that differs from the original protein by predetermined amount. Variant polypeptides containing all amino acid changes at each locus identified in silico or containing a restricted subset of amino acids are separately produced. Each variant polypeptide differs from the unmodified protein at only one amino acid. In dependent claims, variant proteins containing modifications from two or more different LEADs are produced and screened.

Each rejected claim requires that each of the polypeptides that is generated differs from the original polypeptide by only one residue, and requires that each polypeptide is produced separately and screened separately. Each claim requires that sets of candidate lead **proteins** are produced. Each candidate LEAD protein contains a single amino acid replacement.

Differences between the disclosure of Winter and the rejected claims

Winter discloses altered antibodies that have a heavy and light chain in which at least part of the CDRS in the light and heavy chain variable domains are placed by analogous parts of CDRs from a different antibody. In the particular embodiment, described in Example 3, relied upon for the rejection by the Examiner, an antibody to the antigen Campath-1 was

modified by "reshaping" the light and heavy variable domains by transfer of the CDRs to a human backbone and then modification of one or two residues in the CDR to restore the 3-D structure.

The starting material was a rat IgG2a Campth-1 antibody designated YTH 34.5HL-G2B. The heavy and light chain variable domains were cloned and sequenced. The hypervariable regions of YTH 34.5HL were mounted on human heavy or light chain framework regions.

In stage 1 of the process for humanizing the antibody, the reshaped heavy chain variable domain (HuVHCAMP) was attached to constant domains of the rat isotype IgG2 b and transfected into a heavy chain loss variant of the YTH34.5 hybridoma and expressed. The cloned rat heavy chain variable domain also was expressed in the same way. Antibodies were harvested and tested. It was found that the antibody with the human heavy chain domain bound poorly to the Campath-1 antigen and was weakly lytic. This was ascribed to a change in folding that occurred in the humanized version of the antibody. In HuVHCAMP, Phe27 is replaced by Ser because of the human heavy chains that were used. To restore the structure, the Ser27 was mutated back to a Phe. Similarly, the Ser30 also was changed to Thr. Thus, two mutants were produced: **one** with a **single** mutation (Ser27 to Phe), and another with the double mutation Ser27 to Phe **and** Ser30 to Thr to restore the structure of the antibody.

This is clearly not a disclosure of a highthroughput method of protein evolution, but is merely providing a mutation of a modified protein to restore the original function. There are numerous differences between the steps of the procedure in which Winter generated a humanized Campth-1 antibody from the rat antibody. **(1)** Claim 28 requires a high throughput method. The modification of the antibody as described by Winter did not involve high throughput screening. Two polypeptides were produced: one have a single amino acid change and another having two amino acid replacements. **(2)** Claim 28 also requires preparation of nucleic acid molecules encoding variant proteins, where each variant nucleic acid encodes a candidate LEAD mutant protein that **differs by one replacement amino acid** at one is-HIT target locus from the target protein. In Winter only **one** mutant with a single amino acid change was produced. The second mutant contained two modifications. Winter does not disclose preparing nucleic acid molecules encoding **variant proteins**, but only discloses making a single modified protein with one amino acid change. **(3)** Claim 28 also requires that the amino acid **residues** at each of the identified is-HIT target loci in the target

protein is replaced with all of the non-native amino acids, or the amino acid residues **at each of the identified is-HIT target loci in the target** is replaced with a restricted subset of the remaining 19 non-native amino acids. Winters identifies two residues for modification and replaces only one of the loci with one amino acid; the second residue is not replaced by itself, but rather a double mutant is produced. **(4)** Claim 28 requires at step (c) separately introducing the nucleic acid **molecules encoding each candidate LEAD** protein into hosts for expression thereof, and expressing the nucleic acid molecule**s** encoding each variant protein to produce **sets** of candidate LEAD protein**s**, where each candidate LEAD protein **contains a single amino acid replacement, and differs from the target protein by one amino acid replacement**. As discussed, Winter makes only one modified protein with a single amino acid changes. Winters does not disclose producing nucleic acid molecules encoding **each** LEAD nor does Winter disclose producing **sets** of candidate LEAD **proteins**, where each LEAD contains a single amino acid replacement.

Winter does not disclose or describe any highthroughput methods, nor any methods of directed evolution. Winter discloses generation of only one variant protein that differs from a starting protein by one replacement amino acid. Winter is not directed to methods of directed evolution nor methods of high throughput screening, but is directed to methods for preparing humanized antibodies. In one embodiment, Winters happens to make and a test a modified antibody that has a single amino acid replacement. There is no disclosure in Winter for generating a plurality of variants (LEADs) that contain a single amino acid substitution at one of the identified residues (is-HIT target loci), such that each variant (LEAD) differs from the target protein by one amino acid replacement. Thus, Winter does not disclose all elements as claimed. Therefore, Winter does not anticipate any of claims 28 or 30-35.

THE REJECTION OF CLAIMS 1-7, 9-11, 15-18, 36-38, 53-55, 79 and 81 UNDER 35 U.S.C. §103(a)

Claims 1-7, 9-11, and 15

Claims 1-7, 9-11, and 15 are rejected under 35 U.S.C. §103(a) as being unpatentable over Winter as applied to claims 28, and 30-35 above, in further view of Chiang *et al.*, which teaches arrays for systematic analysis. The Examiner states that Winter teaches a method of generating a protein having a predetermined property, but does not teach use of an array, and that the only difference between claim 28 and claim 1 is the use of arrays. The Examiner concludes that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the mutagenesis study of Winter by use of the

array methods of Chiang *et al.* where the motivation would have been that the array methods of Chiang *et al.* allow for a more systematic means for comparing and analyzing different mutants (see, for example, pages 140-141 of Chiang *et al.*)

This rejection respectfully is traversed.

Relevant law

In order to set forth a prima facie case of obviousness under 35 U.S.C. § 103 the combination of the cited references must actually teach or suggest the claimed subject matter. Further, that which is within the capabilities of one of ordinary skill in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. `

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 USPQ 1783 (Fed. Cir. 1992). There must be a reason why a person of ordinary skill in the art would have combined the elements as claimed. KSR v. Teleflex, Inc. 127 S.Ct. 1727 (2007).

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

References within the statutory terms of 35 U.S.C. § 103 qualify as prior art for an obviousness determination only when analogous to the claimed invention. In re Clay, 966 F.2d 656, 658 (Fed. Cir. 1992). Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular problem with which the inventor is involved. In

re Deminski, 796 F.2d 436, 442 (Fed. Cir. 1986); see also In re Wood, 599 F.2d 1032, 1036 (CCPA 1979) and In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

Rejected claims:

Independent claim 1 is directed to a high throughput method for generating a protein or peptide molecule having a predetermined property or activity by:

> (a) identifying, within a target protein or peptide, **a plurality of target amino acids** amenable to providing the predetermined property or activity upon amino acid replacement, wherein:
>
> the identifying of the one or more target amino acids in step a) is conducted *in silico*; and
>
> each target amino acid locus is designated an *in silico*-HIT (is-HIT);
>
> (b) **identifying replacement amino acids** to replace the residue at each is-HIT, wherein:
>
> the replacement amino acids comprise all of the 19 remaining non-native amino acids or a restricted subset of amino acids up to all 19 remaining amino acid; and
>
> a restricted subset is a group of s amino acids selected to have a predetermined effect on protein activity;
>
> (c) producing a **collection** of sets of nucleic acid molecules that encode **candidate LEAD proteins**, wherein:
>
> each encoded candidate LEAD protein contains a single amino acid replacement;
>
> each nucleic acid molecule in a set encodes the same candidate LEAD protein;
>
> each candidate LEAD protein differs by one amino acid from the target protein or peptide, whereby the encoded candidate LEAD proteins in each set differ by one amino acid from the encoded candidate LEAD proteins in each of the other sets;
>
> each set is separate from each and all other sets;
>
> (d) individually introducing each set of nucleic acid molecules into host cells and **expressing the encoded candidate LEAD proteins** to produce **sets of LEAD proteins,** whereby:
>
> each candidate LEAD protein in a set contains the same amino acid replacement;
>
> the host cells comprise an addressable array such that each LEAD protein is expressed at a different locus in the array, and the identity of each candidate LEAD protein at each locus is known; and
>
> (e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity of an unmodified target protein, wherein each such identified protein is designated a LEAD mutant protein.

Dependent claims recite particulars of the methods.

Claim 1 and dependent claims, thus, require a high throughput method, identification of a plurality if is-HITs, identification of replacement **amino acids** for each is-HIT, production of a **collection** of **sets** of nucleic acid molecules that encode a **plurality** of

candidate lead proteins, where each LEAD differs by only one amino acid from the original target, and expressing the LEAD proteins, and screening each LEAD. The methods of claim 1 and dependent claims also require that the host cells comprise an addressable array such that each LEAD protein is expressed at a different locus in the array, **and** the identity of each candidate LEAD protein at each locus is known. Also, claim 1 recites that the nucleic acids in the host cells, and ultimately the encoded proteins, comprise an addressable array, which means that the identity of each protein at or that comprises each locus is *a priori* known. This is a consequence of the methods as claimed. In accord with the claimed methods, single amino acid changes are individually introduced and screened.

Differences between the cited references and the instant claims

Winter

Winter is discussed above. As noted above, Winter does not teach a high throughput method, nor preparation of modified proteins that each contain a single amino acid change compared to a target protein and screening of each such protein. Winter only teaches two modified proteins, only one of which has a single amino acid change. Instant claim 1 recites that a plurality of is-hit residues are identified and proteins (*i.e.*, a plurality) are separately produced with single mutations at each residue. Claim 1 also states that replacement amino acids are identified for each is-HIT. Winter only replaces the Ser30 with Phe, not with replacement amino acids. Winter does not teach producing a collection of nucleic acid molecules that encode a plurality of LEAD proteins. As discussed, Winter is directed to a method for preparing humanized antibodies, and in one embodiment happens to describe replacement of a single amino acid to restore function lost by virtue of selection of the human antibody backbone. The second modified protein produced is double mutant. Winter does not teach or suggest any method of directed evolution nor any high throughput method. Winter does not teach or suggest an addressable array, nor provide any teaching or suggestion to have employed an addressable array, since only two modified proteins were prepared.

Chiang *et al.*

Chiang *et al.* teaches the use of arrays for *in vivo* analysis of bacterial virulence. Chiang *et al.* is a review article describing various bacterial screening assay systems to identify the function of bacterial genes and is of little relevance to the instant claims. Chiang *et al.*, but does not teach or suggest a high throughput method of directed evolution in which is-hit residues are identified and sets of proteins each differing by one amino acid from the

original target protein are produced and screened. Chiang *et al.* does not teach or suggest an addressable array such that member of a collection is expressed at a different locus in the array, and the identity of each candidate LEAD protein at each locus is known. Thus, Chiang *et al.* does not cure the deficiencies in the teachings of Winter nor even add the element of an addressable array.

Analysis

The combination of teachings of Winter with those of Chiang *et al.* does not result the claimed methods of either claim 1 or 28 nor any claim dependent thereon. The combination of teachings of Winter and Chiang *et al.* fails to teach or suggest at least the following elements of the instantly claimed methods: a high throughput method; production of and screening a plurality of candidate LEADS that each contain a single amino acid difference from the target protein; the use of addressable arrays in which each the identify of each protein at each locus is known. As discussed, Winter does not teach or suggest a high throughput method of protein evolution, but rather is directed to a method for humanizing antibodies and in one embodiments prepares a modified antibody that differs in one amino acid from the original antibody. As discussed, this does not suggest identifying a plurality of is-HITs and separately preparing proteins in an addressable array where each protein at each locus differs in one amino acid from the target protein. As noted Winter only prepares one protein that meets this limitation. Chiang *et al.* does not cure any of these deficiencies. Thus, the combination teachings of these references cannot and do not results in the instantly claimed methods. Therefore the Examiner has failed to set forth a *prima facie* case of obviousness.

Furthermore, these references are not even properly combinable. Winter is not directed to a screening method; and only two variant proteins are prepared. The Examiner states Chang *et al.* teaches that "mutagenized bacterial strains are stored individually in arrays (usually in the wells of microtiter dishes).. ," thereby permitting "analysis to be performed simultaneously on a relatively large number of genes during an actual infection." Chiang *et al.*, thus is not even analogous art. References within the statutory terms of 35 U.S.C. § 103 qualify as prior art for an obviousness determination only when analogous to the claimed invention. In re Clay, 966 F.2d 656, 658 (Fed. Cir. 1992). Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the reference still is reasonably pertinent to the particular

problem with which the inventor is involved. In re Deminski, 796 F.2d 436, 442 (Fed. Cir. 1986); see also In re Wood, 599 F.2d 1032, 1036 (CCPA 1979) and In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004).

Chiang *et al.* is from a different field of endeavor from Winter. Chiang *et al.* is directed to screening bacterial for virulence; Winter is directed to methods for making humanized antibodies. Their subject matter is completely different, and, thus, they are not even properly combinable. Further, Chiang *et al.* (similarly Winter) is not pertinent to the instant claims, which are directed to methods of directed evolution or proteins.

As discussed above, Winter fails to teach or suggest numerous elements of the instant claims, which are not cured by the teachings of Chiang *et al.* Winter is directed to a method for humanizing antibodies and prepares two modified proteins. Winter is not screening large numbers of proteins or genes, but is constructing humanized antibodies. There is nothing in the Winter that suggests a reason to perform simultaneous analysis on proteins or on genes. Chiang *et al.* is directed to analysis of bacterial virulence and screens large numbers of genes. There is nothing related in these references, and no reason to combine them. The subject of each is unrelated to the other and there would be no reason to use an array to screen two proteins. As noted Chiang *et al.* fails to teach or suggest the use of addressable arrays. Therefore, the Examiner **has failed to set forth a *prima facie*** case of obviousness.

Notwithstanding the failure to set forth a *prima facie* case of obviousness, neither reference, nor any cited reference, singly or in combination teaches or suggests that methods as claimed in this application could be so powerful. As discussed in the previous response, the instantly claimed methods are quite powerful, in that proteins with very few, in fact, single amino acid changes, with striking changes in properties can be identified. The specification, exemplifies application of the methods to interferons.. To date the method has been applied to 1000s of proteins, and candidate LEADS have been identified and are being pursued as therapeutics. A company, the assignee of the instant application, was founded and has successfully developed evolved therapeutic proteins employing this method. None of the cited references nor references of record teach or suggest a method in which amino acids are individually and separately replaced, and the variants separately produced and separately screened. To be clear, as claimed, the method is performed with addressable arrays so that a multitude of proteins are prepared and screened in parallel (in parallel). The **DECLARATION Dr. Vega**, a joint inventor, provided in the previous response describes the success of these methods and evidences the power of the method in identifying LEAD

compounds that exhibit a predetermined property. Identified LEADS, with a predetermined property, exhibit the property with as few as a single amino acid replacement. The power of the method derives from the semi-rational systematic unbiased method in which by virtue of changing amino acids one-by-one and testing them one-by-one, all changes are equally represented and tested. As a result, LEAD proteins, which exhibit a significant change in a property, can be developed contain as few as single amino acid change, and retain therapeutic activity.

As discussed in the previous response the DECLARATION of Dr. Vega, provided in the previous response, demonstrates the power of the instantly claimed methods. The method is quite powerful and has been used successfully to identify a large number (i.e. thousands) of candidate LEAD proteins that are evolved to possess a predetermined property or activity with a minimal number, as few as one, of amino acid changes. The resulting proteins retain the original activity. As described in the DECLARATION, the method has resulted in the identification of quite a few candidate LEAD protein molecules that possess a predetermined property or activity and retain an original activity of the unmodified polypeptide. The modified proteins have a minimal number of amino acid changes; the resulting polypeptides retain a desired therapeutic activity, but exhibit a change in a predetermined property. As described in the application and in the DECLARATION, the method is unbiased in that all possible intended variations are produced, there is no bias that results from any selective pressure in effecting the mutations, transducing or infecting host cells, growing the host cells and expressing the encoded protein. Since each is done individually, there is no selection amongst and between variants. The DECLARATION evidences the capacity of the instant method to identify mutant molecules with improved predetermined properties and/or activities. The DECLARATION also shows that the modified proteins retain desired activities/properties.

The DECLARATION describes that the instant method is an extremely powerful method that has been used to identify thousands of candidate LEAD molecules of a target polypeptide evolved to have a predetermined property, using a rational, unbiased approach in which each modified polypeptide is individually produced and screened. Using the methods as claimed in the instant application, LEAD polypeptides with an evolved predetermined property/activity are efficiently and effectively generated. As described in the DECLARATION, using the claimed methods, Nautilus Biotech, under the guidance of Manuel Vega and others at the company, has identified valuable candidate proteins for

therapeutic use.

In the DECLARATION, data are provided evidencing that numerous LEAD polypeptides with a predetermined evolved property have been identified. The data show that, using the methods as claimed, hundreds of candidate LEAD polypeptides were identified and screened in each of IFN-alpha, IFN-beta, IFN-gamma, Growth Hormone and erythropoietin based on the predetermined property of protease resistance. The results show that the method as applied reliably and efficiently results in the generation of LEAD polypeptides exhibiting an evolved predetermined property, exemplified as increased protease resistance in the DECLARATION. The data also show that such polypeptides, with the increased protease resistance, have improved pharmacokinetic profiles following subcutaneous and per-oral administration.

The power of the method is evident when one considers that the method as claimed permits the discovery of therapeutic polypeptides, containing in many instances only a single amino acid, that are dramatically altered in the property evolved compared to the native polypeptide. For example, the DECLARATION provides data evidencing that a mutant IFN-α containing only a single amino acid mutation identified by the method based on the predetermined property of protease resistance, when administered subcutaneously or orally, retains anti-viral activity in the serum for a longer time period than the native polypeptide.

In the case of per-oral administration, the native polypeptide retains **no** detectable activity when administered; whereas, the IFN-α with a single amino acid change, identified by the methods herein, can be successfully administered orally. This is really astounding, and of enormous medical and economic value. Therefore, the results provided in the DECLARATION show that the methods as claimed have benefits that are not taught or suggested by any of the cited references. None of the cited references, singly or in any combination thereof, teaches or suggests a method as instantly claimed, in which target amino acids and replacement amino acids are identified *in silico*. None teaches or suggests a method in which mutations are introduced into nucleic acid molecules to individually and separately produce proteins containing only a single change from the original polypeptide. None, singly nor in any combination thereof, teaches that such combination of steps permits directed evolution of proteins to evolve a predetermined property/activity by changing only one or two or very few amino acids.

Claims 36-38

Claims 36-38 are rejected under 35 U. S. C. 103(a) as being unpatentable over Winter as applied to claims 1-7, 9-11, 15, 28, and 30-35 in further view of Alam *et al.* (Journal of Biotechnology, volume 65, 1998, pages 183-1901) because Winter does not teach "Winter does not teach use of proteolysis as a means of digestion" This deficiency is allegedly provided by Alam *et al.*, which allegedly render a portion human growth hormone that is not resistant to proteolysis, and mutate it render it resistant to proteolysis. The Examiner concludes that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the is-Hit generation method of Winter by generating proteolysis resistance mutants, as described in Alam *et al.* where the motivation would have to generate proteins which are expected to have a longer period of bioavailability with characteristic pharmacological importance.

This rejection is respectfully traversed.

The claims

Claims 36-38 are directed to embodiment in which the predetermined property evolved is protease resistance.

Winter

Winter is discussed above. As discussed above, Winter fails to teach or suggest several elements of the claims

Alam *et al.*

Alam *et al.* teaches that the region from amino acids 134-150 hGH is cleaved by plasmin and thrombin and describes an hGH mutant (Arg to Asp at 134 and Thr to Pro at 135) that is resistant to proteolytic cleavage by thrombin. Alam *et al.* provides no teachings or suggestions regarding rational methods of protein evolution nor one in which amino acids are modified and the variant proteins tested one-by-one nor a method in which the variants are produced in addressable arrays such that the identity of each variant at a locus is known. Thus, Alam *et al.* fails to cure the deficiencies in the teachings of Winter *et al.*

The combination of teachings of Winter and Alam *et al.* does not result in the instantly claimed methods

The combination of teachings of the references fails to teach or suggest a method that includes the above noted steps, including modifying one amino acid at a time and expressing and screening each modified protein separately to identify LEADs that differ from the

original protein at one locus. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

Claims 16-18, 53-55, and 81

Claims 16-18, 53-55, and 81 are rejected under 35 U. S. C. 103(a) as being unpatentable over Winter in view of Chiang *et al.* as applied to claims 1-7, 9-11, 15, 28, and 30-35 further in view of Alam *et al.* This rejection respectfully is traversed.

As discussed above, the combination of Winter *et al.* in view of Chiang *et al.* does not result in any of the claimed methods. Alam *et al.* as discussed above fails to cure these deficiencies.

Claims 79

Claim 79 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winter in view of Chiang *et al.* as applied to claims 1-7, 9-11, 15, 28, and 30-35 above, and further in view of Jones *et al.* (CAMS, volume 8, 1992, pages 275-282), which shows PAM matrices and states that it is the authors "hope that the matrices presented here will more clearly express the general nature of the underlying amino acid similarities." The Examiner concludes that:

> [i]t would have been obvious to someone or ordinary skill in the art at the time of the instant invention to modify the is-HIT generation method of Winter and Chiang *et al.* by further use the PAMs described in Jones *et al.* where the motivation would have been that applying the site directed mutagenesis study to the claimed analysis condition of PAM matrices yields a clearer and more efficient understanding of the amino acid residues comprising the protein of interest (see for example, page 276 of Jones *et al.*).

This rejection respectfully is traversed.

Analysis

The deficiencies in the teachings of Winter *et al.* in view of Chiang *et al.* are discussed above. Jones fails to cure these deficiencies. Therefore the combination of teachings of these references does not result in any of the claimed methods. Thus, the Examiner has failed to set forth a *prima facie* case of obviousness.

THE REJECTION OF CLAIMS 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6-16, and 19 of copending Application No. 11/707,014 because claims of the copending application:

are a species of the generic claims listed in the instant application, and therefore the claims of '014 anticipate the claims of the instant application. While both sets of claims are drawn to identifying LEAD or super-LEAD proteins that possess a desired activity, '014 has the additional limitation of choosing the is-HITs based on structural parameters

This rejection respectfully is traversed.

Relevant law

Obviousness-type double patenting occurs when the difference between a first-patented invention and a later claimed invention involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. See, e.g., General Foods Corp. v. Studiengesellschaft Kohle mbH, 23 USPQ2d 1839, 1845 (Fed. Cir. 1992). Analysis for obvious-type double patenting involves a comparison of the claims at issue "with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference." Id. (emphasis in original); see, also, Ortho Pharm. Corp. v. Smith, 22 USPQ2d 1119, 1125 (Fed. Cir. 1992) ("It is the claims, not the specification that defines an invention [citation] . . . [a]nd it is the claims that are compared when assessing double patenting."). ***Thus, an obviousness-type double patenting rejection is based on the claims and not on the disclosure of a patent.***

The comparison between claims in an obviousness-type double patenting inquiry requires the use of a fundamental rule of claim construction, that the invention is defined by the claim taken as a whole – every claim limitation (or each step) being material to the description of the invention. Ortho Pharm. Corp., 22 USPQ2d at 1125. Thus, it is inappropriate to base an obviousness-type double patenting rejection on the disclosure of a patent, even when such disclosure is found in the claims. Only the claims are considered in determining whether obviousness-type double patenting exists and they are not used as disclosure but are interpreted based on the rules of claim construction.

Obviousness-type double-patenting has not been found when claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue. See, e.g., Id. In Ortho, obvious-type double patenting was not found in an instance in which the claims in the patent at suit were directed to compounds that did not encompass, structurally, the compounds claimed in the prior patents, and the claims in the prior patents did not suggest a modification (based upon the principles of claims interpretation) of their

compounds to produce compounds claimed in the patent at suit.

Analysis

The Examiner states indicated that the claims of copending U.S. Application Serial No. 11/707,014 are species of the instant claims. This is not necessarily correct. The methods claimed in this application and the copending application are different; they are not related as a genus species. Claim 1 of the copending application recites:

> A method for generating a protein or peptide molecule, having a predetermined property or activity, the method comprising:
>
> (a) identifying, within a target protein or peptide or plurality thereof, one or more target amino acids, wherein:
>
> each target amino acid is designated an in silico-HIT (is-HIT); and
>
> **the is-HIT target amino acids are identified by identifying structurally homologous loci between the target protein and a reference protein possessing the desired activity;**
>
> (b) identifying one or more replacement amino acids, specific for each is-HIT, wherein each protein or peptide comprising a single amino acid replacement within the target protein or peptide is designated as a candidate LEAD protein;
>
> (c) producing a population of separate sets of nucleic acid molecules, wherein:
>
> each set encodes a different candidate LEAD protein;
>
> all nucleic acid molecules in a set encode the same protein;
>
> each candidate LEAD protein contains a single amino acid replacement; and
>
> each set of nucleic acid molecules encodes a candidate LEAD protein that differs by one amino acid from the target protein or peptide;
>
> (d) separately introducing each set of nucleic acid molecules into host cells and expressing the encoded candidate LEAD proteins, wherein the host cells are addressably arrayed; and
>
> (e) individually screening each set of encoded candidate LEAD proteins to identify one or more proteins that has an activity that differs from an activity an unmodified target protein, wherein each such protein is designated a LEAD mutant protein.

Dependent claims recite that the predetermined activity is increased resistance to proteolysis.

The claims in this application differ from the claims of the copending application in that in the instantly claimed methods, hits are identified *is silico*, whereas in the copending application they are identified by structural homology between the target protein and a reference protein. The instantly claimed methods are directed to the "2-D" method in which hits are identified in a protein by an *in silico* method; the identified hits are then substituted with replacement amino acids that are all remaining 19 amino acids or amino acids that are amenable to conferring the desired property . In the copending application, hits are identified by structural homology by comparison of the 3D structure of the target protein with

a reference protein that possesses the desired activity. Replacement amino acids are not limited to those that are a restricted subset but can be one or more amino acids. The instant claims are limited to determining hits by *in silico* methods; there is no required comparison with a reference protein, but replacement amino acids are specified. Thus the claims in the copending application are not a species of the instant claims, since they are broader in some aspects (selection of replacement amino acids) and more specific in other aspects.

In addition, it respectfully is submitted that obviousness-type double patenting cannot be properly assessed until there is allowable subject matter. Claims in the copending application may be amended during prosecution, and obviousness-type double patenting will need to be assessed based on the final version of the claims. Thus, deferral of resolution of this issue respectfully is requested.

THE REJECTION OF CLAIMS 1, 4-11, 15 AND 79-81 UNDER 35 U.S.C. §102(f)

Claims 1-7, 9-11, 15-18, 28, 30-38, 53-55, 79 and 81 are rejected under 35 U.S.C. §102(f) because co-pending application U.S. Application Serial No. 11/707,014 10/658,834 allegedly contains claims that are not patentably distinct from the instant application. This rejection respectfully is traversed.

First, patentable distinctness or indistinctness is not a basis for concluding that inventorship is in error. The Examiner urges that the claims in the copending application are species of the instant claims. While not agreeing with that assessment, there is no rule or requirement that inventorship of species be the same as inventorship of a genus.

Second, his rejection has been previously set forth and addressed in a prior action. At that time the claims in the co-pending application were pending in U.S. application Serial No. 10/658,834. U.S. application Serial No. 11/707,014 is a divisional of U.S. application Serial No. 10/658,834 and includes the same claims that were pending and at issue in U.S. application Serial No. 10/658,834.

To set forth a rejection under 35 U.S.C. §102(f), there must be more than a difference in the inventive entity; there must be something more from which in error in naming inventors can be inferred. See In re Katz, 215 USPQ 14 (CCPQ 1982). The issue was addressed in the previous response; the Examiner has provided no reasons or evidence to doubt the original and subsequent review of inventorship.

As stated in the previous response, inventorship of the claims in this application was reviewed with the owner and with inventors of the application to confirm that each named inventor made inventive contributions to one or more of the original claims. A

DECLARATION under 37 C.F.R. §1.132 of Dr. Manuel Vega, stating that inventorship in this application is correct, is of record.

As indicated in the DECLARATION, each named inventor made an inventive contribution to one or more of the original claims in the application. Hugo Ramos Cruz was named as an inventor on this application because of his contributions to the aspect of the methods claimed in this application directed to embodiments in which residues are identified that affect digestion by proteases and are then modified so that they are more digestible (*i.e.*, claims 18 and 19). Thus, inventorship in the instant application is properly named.

* * *

In view of the above, entry of this amendment and examination of the application are respectfully requested.

Respectfully submitted,

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